

# Effects of nutrient deficiencies on the development of restless leg syndrome in pediatric patients with primary malnutrition

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## Relationship between nutritional status and restless legs syndrome

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### Abstract

**Aim:** Although it is emphasized in the literature that conditions such as celiac disease, obesity, and iron deficiency cause an increase in Restless legs syndrome (RLS) incidence, there are not enough studies evaluating the effects of primary malnutrition on the development of RLS. Therefore, in this study, we aimed to evaluate the effects of vitamin and mineral deficiencies on the risk of developing RLS in pediatric patients with primary malnutrition.

**Materials and Methods:** A This study included a total of 100 patients aged 11-18 years who presented to Pediatric Gastroenterology, Hepatology, and Nutrition outpatient clinic and who were diagnosed with malnutrition due to low oral intake between July 2017 and July 2018 and 70 control subjects.

**Results:** The RLS was detected in 18 (18%) in the primary malnutrition group and in four patients (5.7%) in the control group. Anemia, hypoferritinemia, vitamin D deficiency, vitamin D deficiency, folic acid deficiency were significantly more common in the RLS group [P <0.05]. When potential risk factors for RLS development are evaluated according to logistic regression analysis, 30,222 times in patients with anemia; 27,692 times in patients with hypoferritinemia; 29,951 times in patients with vitamin D deficiency; 10.08 times in patients with vitamin D deficiency; 10,615 times in patients with multivitamin deficiency; we detected 3,622 times higher risk of developing RLS in malnourished patients (Table 4). Moderately weak and severe stunting increased the risk of developing RLS 2,971 and 4,670 times, respectively, while severe weak, moderate stunting did not pose a significant risk for the development of RLS.

**Discussion:** Our study shows that malnutrition, anemia, vitamin and mineral deficiencies increase the risk of developing RLS.

### Keywords

Child; Malnutrition; Restless leg; Vitamin

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## Introduction

Restless legs syndrome (RLS) is characterized by neurological events characterized by annoying paresthesia in and irresistible instinct to move legs during sleep or rest. Although it has mostly idiopathic and hereditary occurrence, it may develop secondary to iron deficiency, end-stage renal disorders, pregnancy, rheumatological disorders, diabetes, and neurological disorders such as spinal cord injuries, multiple sclerosis, Parkinson's disease, and polyneuropathy. Its prevalence is reported to be 1-15% [1].

Considering the studies indicating the role of the dopaminergic system in the RLS pathogenesis [1], as well as the key role of iron on the dopaminergic system, malnutrition, as an important cause of iron deficiency, gains importance. Several studies have indicated an increased incidence of RLS in Coeliac disease and iron deficiency [2]. In this study, we also aimed to investigate the relationship between RLS prevalence and nutritional status among patients with malnutrition due to low oral intake, a subject which has sparsely studied so far.

## Material and Methods

**Patient selection:** This study included a total of 100 patients aged 11-18 years who presented to Pediatric Gastroenterology, Hepatology, and Nutrition outpatient clinic and who were diagnosed with malnutrition due to low oral intake between July 2017 and July 2018 and 70 control subjects. All patients and their families gave informed consent prior to study entry. RLS was diagnosed by the criteria established by the International Restless Legs Syndrome Study Group (IRRLS) for the 11-18 age group [3]. The questionnaire assessed RLS diagnostic criteria using 5 questions and those criteria were requestioned using 6 cross questions. Patients meeting all RLS criteria were diagnosed with RLS. In order to confirm the RLS diagnosis, patients meeting the RLS criteria were interviewed via telephone and cross questions were asked. When conflicting answers were obtained from a patient or his/her family during 15-30-minute interviews, this patient was excluded.

### Assessment of nutritional status:

In all patients participating in the study, height was measured without socks and shoes using a calibrated vertical portable stadiometer, to the nearest millimeter. Weight was measured with light clothing using a digital electronic weighing scale, to the nearest decimal fraction of a kilogram. Weight Z score, height Z score, Weight by height (WBH) Z score, body mass index (BMI) Z score were calculated according to age and sex using World Health Organization (WHO) data. Patients with a Z score below -2 in any of the parameters of body weight, height, WBH, BMI were considered as malnourished. Hemogram, vitamin B12, folic acid ferritin, and vitamin-D levels were simultaneously studied.

### Severity of malnutrition was classified as follows [4]:

Moderate underweight: Weight-for-age Z-score  $\geq -3$  SDS to  $< -2$  SDS

Severe underweight: Weight-for-age Z-score  $< -3$  SDS

Normal: Weight-for-age Z-score  $> -2$  SDS

Moderate stunting: Height-for-age Z-score  $\geq -3$  SDS to  $< -2$  SDS

Severe stunting: Height-for-age Z-score  $\geq -3$  SDS

Normal: Height-for-age Z-score  $> -2$  SDS

### Assessment of laboratory parameters

Laboratory studies performed one month earlier were examined. Hemogram, vitamin D, vitamin B12, folic acid, and ferritin levels were examined. The tests that were lacked were performed after patients and relatives were informed and their informed consent was obtained. Local Ethics Committee approved this study.

Serum folic acid, vitamin B12, and ferritin were calculated at 28 °C by a photo multiplier using the electrochemiluminescence method in a Roche Cobas 6000 (601) device and after 18-minute and 27-minute incubation period.

### Levels were defined as follows:

- Vitamin D deficiency,  $< 20$  ng/ml,
- Vitamin D insufficiency, 21-29 ng/ml
- Normal levels of Vitamin D  $\geq 30$  ng/ml. [5]

Ferritin ( $\mu\text{g/L}$ ):  $< 30$  ng/mL was considered hypoferritinemia. [6]

Vitamin B12:  $< 300$  pg/mL was considered vitamin B12 deficiency. [7]

Folate:  $< 4$   $\mu\text{g/L}$  was considered folic acid deficiency. [8]

Multivitamin deficiency: At least two of Ferritin, Vitamin B12, folic acid, vitamin D deficiency, and vitamin D insufficiency were considered multivitamin deficiency

Anemia: A Hemoglobin level less than the age-based normal level was considered anemia

### Exclusion Criteria were as follows:

- Patients below the age of 11 years or above the age of 18 years,
- Patients with chronic conditions other than insufficient intake, which could cause malnutrition, such as Coeliac disease, cystic fibrosis, heart failure, chronic renal failure, cerebral palsy, Down syndrome, chronic diarrhea, malabsorption secondary to bowel surgery, feeding by gastrostomy, inflammatory bowel disease, and diabetes.
- Patients with disorders mimicking RLS, such as positional leg pain, growth pain, tendon, ligament and muscle pain, arthritis, Osgood-Schlatter disease, and patellar chondromalacia.
- Patients that had been treated with vitamin and/or iron within the last three months.

### Statistical analysis:

Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) 22.0 software package was used for all statistical analyses. Study data were expressed as mean  $\pm$  standard deviation, number (n), and percentage (%).

Distribution of quantitative variables was tested using the Kolmogorov-Smirnov test. Those with normal distribution were compared using the Student's t test or one-sided analysis of variance (ANOVA) and those without normal distribution using the Mann Whitney-U test or the Kruskal-Wallis test. Statistical significance was tested with the Chi-square test, the Student's t-test, or the Mann-Whitney U test.

Logistic regression analysis was used to demonstrate any correlation between a dependent variable and one or more independent variables. A p-value of less than 0.05 was considered statistically significant.

## Results

The mean age was  $13.8429 \pm 2.19113$  (11-17) years in the control group and  $13.015 \pm 1.79991$  (11-17.5) years in the malnutrition group. The female-to-male ratio was 2/3 in the control group and 3/2 among the patients with malnutrition. There was no significant difference between the groups with and without RLS with respect to gender distribution ( $P=0.461$ , Table 2). Among 23 patients meeting the RLS diagnostic criteria, five were excluded from the RLS group after cross questions, and 18 (18%) patients with malnutrition were diagnosed with RLS. In the control group, two out of six patients were excluded from the RLS group after questioning with the cross questions and four (5.7%) patients were diagnosed with RLS.

The examination of patients with and without RLS in terms of clinical and laboratory findings revealed that both groups had similar gender distribution. However, Anemia, hypoferritinemia, vitamin D deficiency, vitamin D insufficiency, folic acid deficiency, and multivitamin deficiency were significantly more common in the RLS group ( $P < 0.001$ ,  $P < 0.001$ ,  $P < 0.001$ ,  $P = 0.007$ ,  $P = 0.044$ ,  $P < 0.001$ , respectively). Both groups were similar with regard to vitamin B12 deficiency ( $P = 0.052$ ) (Table 2)

The analysis of the laboratory parameters and the anthropometric measurements between the RLS patients and the controls showed that among patients with malnutrition, RLS patients had a significantly

lower Hb, ferritin, and vitamin D levels ( $P < 0,001$ ,  $P = 0,001$ ,  $P < 0,001$ , respectively) while folate, vitamin B12 serum levels and weight Z score, height Z score, WBH Z score, BMI Z score were similar between those with RLS and without. ( $P = 0,589$ ,  $P = 0,858$ ,  $P = 0,912$ ,  $P = 0,999$ ,  $P = 0,353$ ,  $P = 0,473$ , respectively). In the control group, patients with RLS had significantly lower Hb, ferritin, vitamin D, folate, and vitamin B12 levels compared to those without RLS ( $P = 0,001$ ,  $P < 0,001$ ,  $P = 0,007$ ,  $P = 0,034$ ,  $P = 0,041$ , respectively); there was no significant difference between both groups with respect to weight Z score, height Z score, WBH Z score, BMI Z score ( $P = 0,314$ ,  $P = 0,101$ ,  $P = 0,174$ ,  $P = 0,221$ , respectively) (Table 3).

According to a logistic regression analysis of the risk factors potentially affecting RLS development (ODDS Ratio), the latter was 30.222 times greater in patients with anemia; 27.692 times greater in patients with hypoferritinemia; 29.951 times greater in patients with vitamin D deficiency; 10.08 times greater in patients with vitamin D insufficiency; 3.889 times greater in patients with vitamin B12 deficiency; 14.7 times greater in patients with folate deficiency; 10.615 times greater in patients with multivitamin deficiency; and 3.622 times greater in patients with malnutrition (Table 4). Moderate underweight and severe stunting increased the risk of RLS development by respectively 2.971 and 4.670 times, whereas severe underweight, moderate stunting did not confer a significant risk for developing RLS (Table 4).

**Table 1.** Evaluation of clinical and laboratory features of malnourished patients according to control group

		Control group [70]	Patients with malnutrition [100]	P
Gender:	Female	28 (40%)	60 (60%)	0,010
	Male	42 (60%)	40 (40%)	
RLS		4 (5,7%)	18 (18%)	0,019
Anemia		4 (5,7%)	24 (24%)	0,001
Hipoferritinemia		5 (7,1%)	24 (24%)	0,004
D vitamin deficiency		29 (41,4%)	53 (53%)	0,137
D vitamin Insufficiency		26 (37,1%)	24 (24%)	0,064
Folate deficiency		1 (1,4%)	2 (2%)	0,632
B12 deficiency		6 (8,6%)	6 (6%)	0,519
Lack of multiple vitamins		9 (12,9%)	25 (%25)	0,038

RLS: Restless legs syndrome

**Table 2.** Evaluation of clinical and laboratory findings of patients with and without RLS

		RLS haven't [148]	RLS have [22]	P
Gender:	Female	75(%50,7)	13(%59,1)	0,461
	Male	73(%49,3)	9(%40,9)	
Anemia		12 (8,1%)	16 (72,7%)	<0,001
Hipoferritinemia		13 (8,8%)	16 (72,7%)	<0,001
D vitamin deficiency		61 (41,2%)	21 (95,5%)	<0,001
D vitamin Insufficiency		48 (32,4%)	1 (4,5%)	0,007
Folate deficiency		1 (0,7%)	2 (9,1%)	0,044
B12 deficiency		8 (5,4%)	4 (18,2%)	0,052
Lack of multiple vitamins		18 (12,2%)	16 (72,1%)	<0,001

RLS: Restless legs syndrome

**Table 3.** Evaluation of the differences between the anthropometric measurements and laboratory parameters of the patients with and without RLS.

Patients with malnutrition			
	RLS haven't	RLS have	P
Hb (mg/dl)	13,06±1,24	11,65±2,04	<0,001
Ferritin (µg/L)	41,05±36,66	20,48±16,78	0,001
D vitamin (ng/ml)	21,81±11,54	10,17±5,43	<0,001
Folate (µg/L)	7,90±3,44	8,40±4,026	0,589
VitaminB12 (ng/L)	346,84±147,27	340,12±128,74	0,858
Weight Z score	-2,57±0,35	-2,56±0,47	0,912
Height Z score	-1,85±1,08	-1,85±1,83	0,999
WBH Z score	-0,97±0,82	-0,77±0,89	0,353
BMI Z score	-2,09±0,78	-1,94±0,76	0,473
Control group			
	RLS haven't	RLS have	P
Hb (mg/dl)	13,62±1,36	10,55±0,66	0,001
Ferritin (µg/L)	44,43±30,31	7,3±2,03	<0,001
D vitamin (ng/ml)	23,64±8,94	9,64±5,19	0,007
Folate (µg/L)	7,21±2,52	4,76±1,45	0,034
VitaminB12 (ng/L)	302,36±109,81	160,4±87,11	0,041
Weight Z score	0,59±1,21	-0,08±1,11	0,314
Height Z score	0,07±1,02	0,45±0,32	0,101
WBH Z score	0,66±1,26	-0,38±1,17	0,174
BMI Z score	0,61±1,28	-0,37±1,28	0,221

RLS: Restless legs syndrome, WBH: Weight by height, BMI: Body mass index

**Table 4.** Evaluation of factors that may affect RLS development by logistic regression analysis

	P	ODDS	Confidence interval	Risk
Malnutrition	0.026	3.622	1.169-11.222	+
Anemia	<0.001	30.222	9.975-91.565	+
Hipoferritinemia	<0.001	27.692	9.242-82.976	+
D vitamin deficiency	0.001	29.951	3.923-228.645	+
D vitamin Insufficiency	0.026	10.08	1.317-77.165	+
Folate deficiency	0.031	14.70	1.274-169.581	+
B12 deficiency	0.040	3.889	1.063-14.222	+
Lack of multiple vitamins	<0.001	10.615	3.377-33.366	+
Moderate underweight	0.031	2.971	1.102-8.014	+
Severe underweight	0.876	1.133	0.236-5.441	-
Moderate stunting	0.876	0.912	0.287-2.900	-
Severe stunting	0.007	4.670	1.522-14.335	+

RLS: Restless legs syndrome

## Discussion

Restless leg syndrome has no specific biochemical marker; it is diagnosed on clinical grounds. Studies on adults have suggested that symptoms started at childhood or adolescence in about a third of patients [9]. Some of pediatric studies in the literature have reported a greater RLS prevalence in girls [10,11]. However, as supported by our study, comprehensive epidemiological studies have denied any gender difference for RLS prevalence [12]. Altunayoglu et al. [13] in a domestic adult prevalence study, reported a RLS prevalence of 4.5%. A prevalence study from Kayseri province showed a RLS prevalence of 2.9% among adolescents aged 13-16 years [14]. We demonstrated a RLS prevalence of 5.7% among control patients and 18% in malnutrition patients. We linked our higher RLS prevalence than the literature reports to a smaller sample size, accompanying iron and vitamin deficiencies, and malnutrition. Although Vito et al. [15] reported that RLS prevalence was two times more common in the overweight group compared to the normo-weight group, that difference did not reach statistical significance. In contrast, our study revealed 3.622 times more common RLS prevalence in the malnutrition group compared to the control group ( $P=0.026$ ). Baran et al. [16] demonstrated an increased RLS prevalence in obese adolescents than the control subjects (21.7% vs 1.5%). Our study found an increased prevalence of RLS in patients with malnutrition than the control group (18% vs 5.7%,  $P=0.001$ ). We attributed that difference to a higher prevalence of factors like anemia, iron, and vitamin deficiencies which could alter RLS prevalence among patients with malnutrition. We also noted that vitamin and iron levels that could affect RLS prevalence were not questioned in detail in the majority of studies reporting that obesity increases RLS prevalence [15-17]. Moccia et al. [18] reported that it increased RLS prevalence further among patients with coeliac disease (31% vs 4%), and although there was no significant correlation between RLS and iron metabolism, anemia was more common in patients with coeliac disease and RLS compared to those with coeliac disease but no RLS ( $P=0.003$ ). Işıkay et al. [2] found RLS prevalence as low as 3% in the coeliac group but reported a significant negative correlation between RLS severity and serum ferritin, folate, and vitamin D levels. Our work, on the other hand, found that anemia, low ferritin level, vitamin D deficiency, folate deficiency, and multivitamin deficiency were significantly more common in the RLS group than the control group ( $P<0.001$ ,  $P<0.001$ ,  $P<0.001$ ,  $P=0.044$ ,  $P<0.001$ , respectively). There was no significant difference between both groups with regard to vitamin B12 deficiency (18.2% vs 5.4%,  $P=0.052$ ).

Iron, a cofactor of the enzyme tyrosine hydroxylase necessary for dopamine production, has an important role for RLS pathophysiology; dopaminergic drugs are known to be used for RLS treatment with favorable results being attained in some patients [19-20]. Previous studies indicated a negative correlation between iron deficiency, serum ferritin level and RLS symptom severity [21,22]. We similarly demonstrated that lower serum ferritin level increased RLS development risk by 27.692 folds ( $P<0.001$ ) while anemia increased it by 30,222 times ( $P<0.001$ ). Literature data related to folic acid and RLS are generally limited to adult studies. Lee et al. [23] reported that folic acid levels were lower in patients with RLS compared to those without. Işıkay et al. [2] reported a negative correlation between folic acid level and RLS severity. There are also several studies in the literature suggesting that there is no significant difference between RLS patients and controls with respect to folic acid level. [13,24] Our work revealed a significantly lower serum folic acid level in RLS patients than controls (9.1% vs 30.7%,  $P=0.044$ ). A logistic regression analysis showed that folic acid deficiency increased RLS risk by 14.7 folds ( $P=0.031$ ).

In a study on adult patients with musculoskeletal symptoms, vitamin D deficiency was found significantly more common in RLS patients, with

vitamin D deficiency increasing RLS risk by 5-fold [25]. Another study reported a significant negative correlation between vitamin D levels and RLS [2]. Our study, in line with the previous studies, demonstrated that RLS prevalence was significantly higher among patients with vitamin D deficiency ( $p<0.001$ ) and that RLS risk increased by 29.951 folds among patients with vitamin D deficiency ( $p=0.001$ ).

We also found that moderate malnutrition and severe stunting increased the risk of RLS (2.971 times  $P = 0.031$  and 4.670 times  $P = 0.007$ , respectively).

The limitations of our study include the lack of investigation of sociodemographic properties among correctable causes of malnutrition, as well as of the effects of RLS on sleep-wakefulness. Additionally, RLS prevalence was higher in our study than the normal population, which we attributed to a small sample size, accompanying iron and vitamin deficiencies, and malnutrition.

However, to the best of our knowledge, the importance of our study stems from its status of being the only study investigating the relationship between malnutrition due to low intake and RLS among pediatric patients.

In conclusion, RLS is an important, prevalent condition in the general population, which impairs sleep quality and affects social life in an unfavorable manner. Our study supports the notion that malnutrition, anemia, and vitamin deficiencies, as correctable causes, increase the prevalence of RLS.

## Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

## Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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## Conflict of interest

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